Diagnostic and Therapeutic Challenges

Edited by H. Richard McDonald

Drs. Alexander T. Bui, Bradley S. Rosen, Richard H. Roe, Gregg T. Kokame

This case is submitted by Drs. Alexander T. Bui and Bradley S. Rosen of the Department of Ophthalmology, Kaiser Permanente, West Los Angeles, California. This case is commented on by Drs. Richard H. Roe and Gregg T. Kokame.

Case Report

A 68-year-old man with no significant ocular or medical history was referred for evaluation of vision loss in both eyes over the preceding month. He noted slow, painless blurring in the left eye followed by the right eye ~2 weeks later. Review of systems was positive for a 10-pound weight loss over the preceding 2 months, lower back pain, and nose bleeds occurring ~1 to 2 times a week over the past month.

On examination, blood pressure was 122/86 mmHg, pulse was 91 beats/min, and temperature was 99°F. His best-corrected visual acuity was 20/150 in the right eye and 20/100 in the left eye. Anterior segment examination showed clear corneas and mild nuclear sclerosis in both eyes. The anterior chamber, iris, and intraocular pressures were within normal limits.

Dilated fundus examination showed clear vitreous with intraretinal hemorrhages from the disk to the midperiphery and occasional white-centered hemorrhages (Figure 1, A and B). The retinal vessels were of normal caliber and tortuosity. On examination and by optical coherence tomography (Stratus-OCT, Carl Zeiss Meditec, Dublin, CA), both maculae showed turbid subretinal fluid. Central foveal thickness was found to be 851 μm in the right eye and 507 μm in the left eye (Figure 2, A and B). No retinal defect or vitreomacular traction was noted on examination. Fluorescein angiogram showed normal vascular filling without retinovascular or pigment epithelial leak (Figure 3, A and B). This case is presented for discussion of diagnosis and management.

We asked several experts for their opinion.

Dr. Richard H. Roe (Los Angeles, California):

Dr. Bui presents an interesting case of a 68-year-old man with bilateral vision loss associated with weight loss, lower back pain, and epistaxis. Dilated fundus examination showed scattered intraretinal and white-centered hemorrhages throughout the fundus bilaterally. The retinal vessels were otherwise unremarkable. Large macular detachments with turbid subretinal fluid were seen in each eye. Fluorescein angiogram failed to reveal any vascular abnormalities or leakage from the retinal pigment epithelium (RPE). Optical coherence tomography confirmed the presence of bilateral neurosensory macular detachments.

The presence of white-centered hemorrhages, or Roth spots, provides an initial differential diagnosis. The Roth spot, first described by Moritz Roth in 1872, was once considered a pathognomonic sign of septic emboli secondary to subacute bacterial endocarditis but has since proven to be a much less specific finding. Both Von Barsewisch[1] and Duane et al[2] histopathologically showed that Roth spots are not a cluster of leukocytes, as originally suggested, but rather a platelet–fibrin clot within a ruptured retinal capillary. This explains why Roth spots can be seen in a variety of conditions in addition to endocarditis such as leukemia, multiple myeloma, and Waldenström macroglobulinemia. Roth spots have also been reported in ischemic microvasculopathies in the setting of diabetes, hypertension, and human immunodeficiency virus/acquired immunodeficiency syndrome. Intracranial trauma causing increased venous pressure, as occurs in shaken baby syndrome, can also produce Roth spots.

The presence of bilateral serous macular detachments in conjunction with intraretinal hemorrhages helps to narrow the differential diagnosis even further. This combination of findings has been described in leukemia and plasma cell dyscrasias such as multiple myeloma and Waldenström macroglobulinemia[3–7] but has not been reported in patients with subacute bacterial endocarditis. In addition, fluorescein angiography failed to show a source for the subretinal fluid. This finding in particular (turbid serous macular detachments with no vascular or RPE leaks) is highly suggestive of a plasma cell dyscrasia. The occurrence of serous macular detachments in patients with plasma

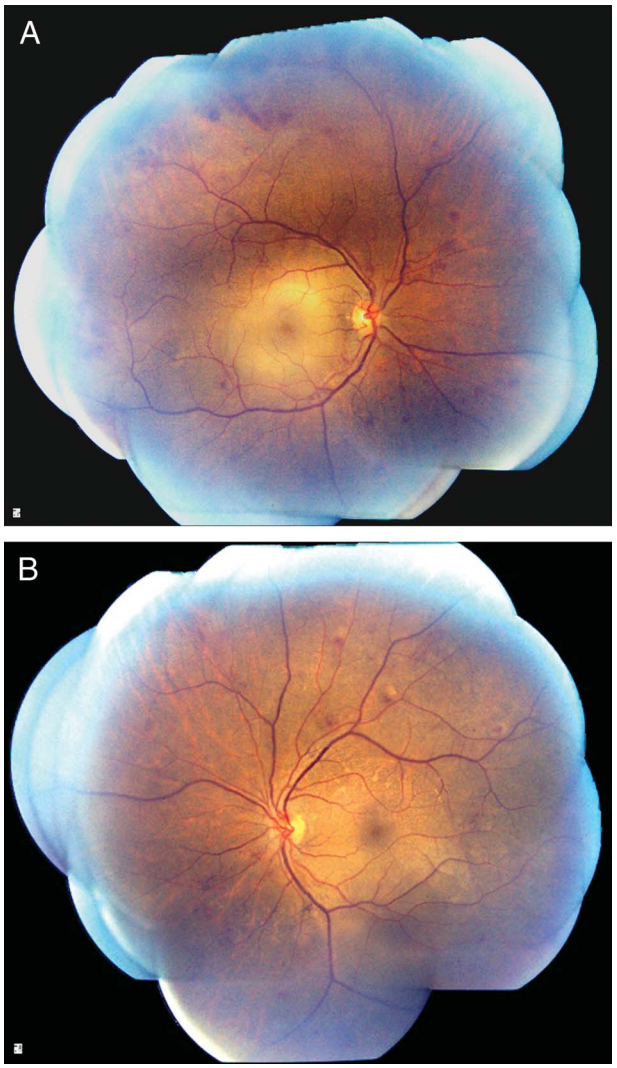

Fig. 1. **A** and **B**, Turbid subretinal fluid and intraretinal hemorrhages.

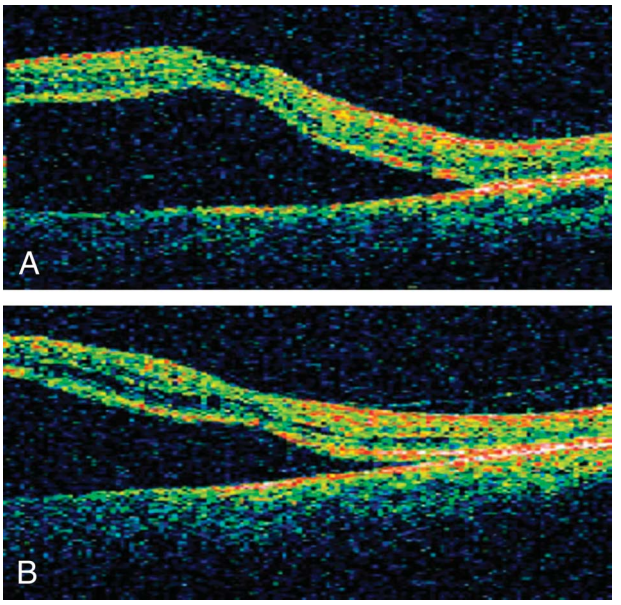

Fig. 2. Central foveal thickness was found to be 851 μm in the right eye (**A**) and 507 μm in the left eye (**B**).

cell dyscrasias has been recognized for some time. Franklin et al[4] provided a detailed clinical and histopathologic description of a young man with multiple myeloma who presented with acute vision loss and bilateral macular detachments. Gass described a similar case with bilateral serous macular detachments in a patient with Waldenström macroglobulinemia.[5] He noted the absence of fluorescein leakage from either the inner or outer blood–retinal barrier. Others have subsequently confirmed the occurrence of these specific findings in patients with both multiple myeloma and Waldenström macroglobulinemia,[6–8] and immunohistopathologic studies have identified immunoglobulins in the subretinal space in patients with these disorders.[9,10] Presumably, the high circulating levels of abnormal serum proteins in these patients somehow gain entrance to the subretinal space osmotically pulling fluid into the subretinal space. Further evidence to support such a hypothesis comes from the observation that macular detachments in patients with plasma cell dyscrasias have been reported to resolve completely after plasmapheresis.[5] Ho et al have appropriately termed this a transudative macular detachment as opposed to an exudative macular detachment such as the one that might be seen in Vogt-Koyanagi-Harada disease, exudative age-related macular degeneration, central serous retinopathy, malignant hypertension, posterior scleritis, sympathetic ophthalmia, or leukemia, among other conditions in which fluorescein angiography will show one or more pinpoint leaks in the RPE.

The reason for no vascular or RPE leaks seen on fluorescein angiography in patients with plasma cell dyscrasias and serous retinal detachment is unknown. Of note, however, Ogata et al[8] reported on a patient with macroglobulinemia who presented with both RPE and serous macular detachments. Fluorescein angiography failed to show either RPE leaks or pooling of dye in the sub-RPE space, which suggested that the lack of fluorescein leakage or pooling in these patients was likely secondary to blockage of fluorescein dye by the abnormal accumulation of immunoglobulins in the subretinal and sub-RPE spaces.

Dr. Bui's patient seems, therefore, to have posterior segment complications related to a plasma cell dyscrasia. The patient should, therefore, undergo a complete physical examination seeking specifically for hepatosplenomegaly as well as mucosal and skin petechiae and purpura. Laboratory investigations should include

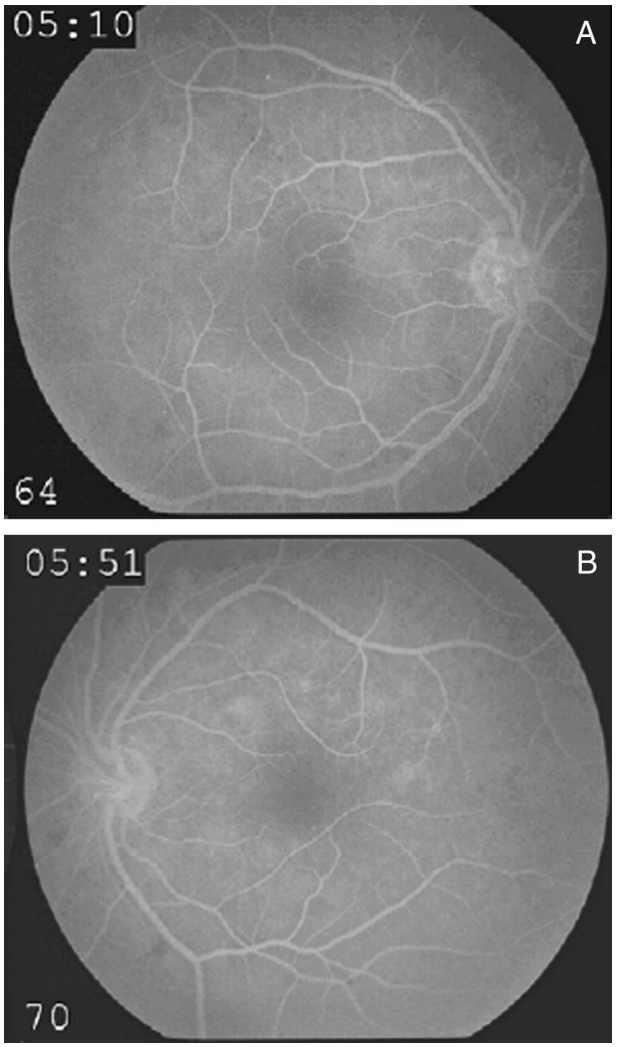

Fig. 3. **A** and **B,** Fluorescein angiogram showed normal vascular filling without retinovascular or pigment epithelial leak.

a complete blood count with differential, a peripheral blood smear, and serum protein electrophoresis. Other tests to be considered include a bone marrow biopsy and x-ray films to look for lytic lesions.

Dr. Gregg T. Kokame (Honolulu, Hawaii):

This 68-year-old man presents with bilateral exudative retinal detachments, which involve the macula and have occurred recently over a 1-month period based on symptoms. On the fundus photographs, there is significant turbid subretinal fluid, which is echolucent on optical coherence tomography evaluation in both eyes. On optical coherence tomography evaluation, there is also some intraretinal edema in the detached retina, which is worse in the left eye. In addition, there are prominent peripheral retinal hemorrhages.

Bilateral exudative macular detachments can occur associated with a number of systemic diseases or treatments. Acute hypertension can lead to hypertensive choroidopathy, secondary exudative macular detachments, and peripheral retinal hemorrhages. However, this patient's blood pressure was in the normal range. Severe bullous retinal detachments can also occur associated with idiopathic central serous chorioretinopathy, often but not always associated with the use of systemic steroids. This patient was not taking systemic steroids and shows no evidence of RPE leakage in the macular region characteristic of idiopathic central serous chorioretinopathy. However, macular detachments can less commonly be associated with peripheral RPE leakage, and it would be important to get peripheral views on the fluorescein angiogram. In addition, the subretinal fluid is usually clear in idiopathic central serous chorioretinopathy, not turbid like in this case. Systemic lupus erythematosus can also present with serous retinal detachment and an idiopathic central serous chorioretinopathy-like picture and could also cause a microvasculopathy resulting in the retinal hemorrhages.

Serous retinal detachment can also occur in uveitis such as Harada disease, but there were not any signs of inflammation on examination or the typical pinpoint RPE leaks on fluorescein angiography. Ultrasound in Harada disease would show marked thickening of the retina–choroid layer. Uveal effusion syndrome can also present with bilateral retinal detachment and is related to abnormal thickening and infiltration of the sclera with disorganization of the collagen bundles within the sclera and proteoglycan deposition. Nanophthalmos can also cause bilateral exudative detachments in hyperopic small eyes.

This particular patient presented with systemic findings, including nose bleeds and lower back pain starting at about the same time as the visual findings. Exudative macular detachments have also been reported as an initial presenting finding associated with hyperviscosity syndromes and multiple myeloma.[6] Multiple myeloma is related to plasma cell tumors, in which there is a proliferation of a single clone of immunoglobulin-secreting plasma cells. Systemic findings in multiple myeloma can include mucous membrane bleeding, which could explain the epistaxis, and bone pain from lytic lesions within the bone, which could explain his lower back pain. The diagnosis is based on electrophoresis of the serum or urine identifying a monoclonal gammopathy. These patients also have hyperviscosity and can present with marked retinal congestive vascular disease, which results in venous engorgement and tortuosity. This is not seen in this case, but the retinal hemorrhages could be explained in relation to multiple myeloma. The proteinaceous material in the subretinal fluid in these cases with multiple myeloma have been identified as immunoprotein based on the immunoperoxidase technique.[9]

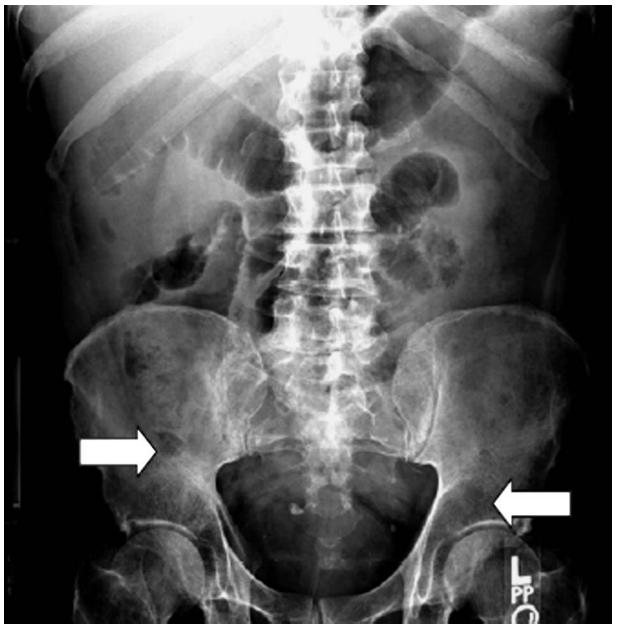

Fig. 4. The x-ray plain films showed multiple lytic lesions of the bony pelvis.

Further testing in this patient would thus include serum protein electrophoresis, urine protein electrophoresis for Bence-Jones proteins, and radiologic studies of bones for lytic lesions. If the results are diagnostic for multiple myeloma, treatment would involve chemotherapy, which may allow some gradual resolution of the exudative retinal detachments.

Editor's Note:

Dr. Bui presents a 68-year-old man with decreased vision in both eyes, weight loss, back pain, and epistaxis. This patient had multiple white-centered hemorrhages and turbid subretinal fluid and was found to have no leakage on fluorescein angiography.

Our consultants, Drs. Roe and Kokame, have provided a discussion of this case. Dr. Roe begins with comments concerning the Roth spots noted in this man and gives a differential diagnosis of such lesions.

I. Endocarditis
II. Leukemia
III. Multiple myeloma
IV. Waldenström macroglobulinemia
V. Ischemic microvasculopathies
  A. Diabetes
  B. Hypertension
  C. Human immunodeficiency virus/acquired immunodeficiency syndrome
  D. Intracranial trauma
1. Shaken baby syndrome

Dr. Kokame emphasizes the differential diagnosis of exudative macular detachments.

I. Acute hypertension
II. Idiopathic central serous retinopathy
III. Systemic lupus erythematosus
IV. Vogt-Koyanagi-Harada syndrome
V. Idiopathic uveal effusion syndrome
VI. Hyperviscosity macroglobulinemia
  A. Waldenström macroglobulinemia
  B. Multiple myeloma

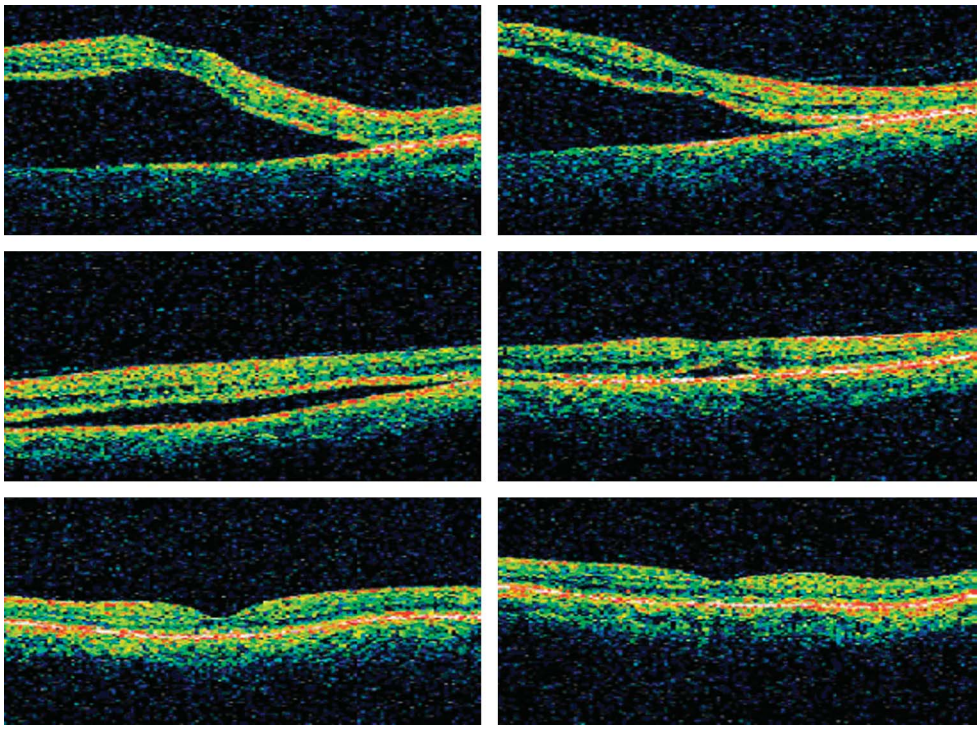

Fig. 5. Optical coherence tomography at presentation (**A**), 2 months (**B**), and 4 months (**C**) after initiating plasmapheresis and chemotherapy for multiple myeloma.

Table 1.

Lab	Value	Reference
APTT	48	(22–36 sec)
INR	>10.0	0.8–1.2
WBC's	99	4.0–11.0 thou/cumm
HGB	7.4	14.0–18.0 g/dL
HCT	23.8	42–52%
PLT's	54	130–400 thou/mcL
SPEP	IgA 9270	139–347 mg/dL

Both Drs. Roe and Kokame focus in quickly on the possibility that plasma cell dyscrasia is at the heart of this case. Dr. Roe emphasizes the importance of the absence of fluorescein dye leakage despite the finding of turbid subretinal fluid. He notes immunohistopathologic studies showing immunoglobulins in the subretinal space in these disorders. The circulating abnormal serum proteins gain access to the subretinal space and then seem to block underlying hyperfluorescent dye leakage.

Dr. Kokame notes that multiple myeloma is related to plasma cell tumors and that systemic findings in multiple myeloma include mucous membrane bleeding explaining the patient's epistaxis. The lower back pain experienced by the patient might be caused by lytic lesions within the bone.

Our consultants have recommended the following evaluations with some testing based on early results.

I. Physical examination
   A. Hepatosplenomegaly
   B. Mucosal, skin petechiae
II. Laboratory investigation
   A. Complete blood cell count with differential
   B. Peripheral blood smear
   C. Serum protein electrophoresis
   D. Urine protein
1.Bence-Jones protein
III. Additional evaluation if needed
   A. Radiologic evaluation
1. Lytic bone lesions
   B. Bone marrow biopsy

The treatment for multiple myeloma would involve chemotherapy, which would result in gradual resorption of the exudative material causing the subretinal detachments.

We have asked Dr. Bui for follow-up on this case.

Follow-Up

Initial laboratory examination included complete blood count with differential, chemistry panel, hemoglobin A1C, international normalized ratio, activated partial thrombin time, and serum electrophoresis. The chemistry panel and hemoglobin A_1C were normal (Table 1).

The patient was referred to the hematology–oncology service where he was diagnosed with IgA-κ multiple myeloma. He was admitted for transfusions of blood and platelets. The x-ray plain films showed multiple lytic lesions of the bony pelvis (Figure 4). Results of a bone marrow biopsy showed plasma cells constituting 90% of marrow cells virtually replacing myeloid and erythroid precursors. He was started on plasmapheresis therapy, steroids, and thalidomide.

He returned to the retina service 1 month after discharge with reports of improved vision. The best-corrected visual acuity was 20/100 in the right eye and 20/50 in the left eye. The retinal examination showed decreased subretinal fluid in both eyes. At last follow-up, the vision was 20/30 in the right eye and 20/60 in the left eye with complete resolution of the macular fluid on optical coherence tomography (Figure 5, A–C). The patient later died of pneumonia related to his underlying illness.

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